S. HRG. 99-367, Pt. 2

DRUG EXPORT REFORM

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-NINTH CONGRESS

FIRST SESSION

ON

PROPOSED LEGISLATION TO AMEND THE FEDERAL FOOD, DRUG AND COSMETIC ACT TO AUTHORIZE THE EXPORT OF NEW DRUGS AND BIOLOGICALS NOT YET APPROVED IN THE UNITED STATES TO COUNTRIES THAT HAVE APPROVED THEM

JUNE 5, 1985

PART 2

ADDENDUM

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ADDENDUM
to
DRUG EXPORT REFORM

PMA ANALYSIS OF DRUGS MENTIONED BY
DR. SIDNEY M. WOLFE AT JUNE 5, 1985 EXPORT HEARING

In his testimony on June 5, 1985, before the Senate Labor and Human Resources Committee, Dr. Sidney M. Wolfe cited 19 products allegedly removed from an overseas market to show that the current U.S. ban on the export of drugs not approved by the Food and Drug Administration should not be lifted.

Thirteen of the 19 drugs mentioned by Dr. Wolfe were approved in the 1950s and 1960s, at the very beginning of the modern era of drug regulation. These outdated examples were described in congressional testimony in 1973, again in 1979, and once more by Dr. Wolfe on June 5, 1985. Approval of these 13 drugs as long as 30 years ago has absolutely no bearing on the regulatory capabilities of sophisticated drug-approval authorities operating in the 1980s. Approval of these drugs tells as little about foreign drug-approval authorities today, in fact, as approval of the hundreds of pre-1962 drugs removed from the market under the Drug Efficacy Study Implementation (DESI) program tells about the FDA today.

In addition, based on the best information PMA could obtain, three of the 19 drugs mentioned by Dr. Wolfe were never approved for marketing and were never marketed in any country at any time. One was actually approved by the FDA and marketed in the U.S.

Comparing the experience in Great Britain and the U.S., Dr. Wolfe asserted that "the standards for drug approval are more stringent in this

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country and that allowing exports of unapproved drugs is truly a double standard."

However, in a study in the May 1984 issue of Clinical Pharmacology and Therapeutics (a copy of which is attached), Drs. Olav M. Bakke, William M. Wardell and Louis Lasagna found that the record of drug discontinuations in the U.S. and the U.K. were "remarkably similar" in the most recent decade studied--from 1974 to 1983. In that period, four drugs were discontinued in the U.S. and three were discontinued in the U.K. (even though more drugs were approved in the U.K.). For both the U.S. and the U.K., "drugs that were subsequently discontinued in light of safety questions represent only 2% of the drugs introduced on the market" during the 1970s.

"It appears," the authors stated in comparing the U.S. and the U.K. drug-approval systems, "that drugs approved under modern regulations are seldom associated with unacceptable toxicity, and that the U.S. system of approval, in spite of its greater restrictiveness and insistence on detail, has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions."

A January 1984 FDA study, New Drug Introductions, Discontinuations, and Safety Issues in the United States and the United Kingdom 1960-1982, reached the same conclusion. "Only 14 of the 614 NCEs introduced since 1960 were the subject of documented safety discontinuations on the U.S./U.K. two-country market," the study stated. "These 14 NCEs accounted for eight

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safety discontinuations in the U.S. and 10 safety discontinuations in the U.K." The study further stated: "The conclusion that documented major safety issues are not the primary reason for large differences in discontinuation rates demonstrates the need to closely examine other factors that may be accounting for the differences." (Emphasis added.) (A copy of the study summary is attached, together with an FDA graph depicting drug availability, introductions and withdrawals in the two countries.)

Dr. Wolfe criticized the two studies on the grounds that they "blur the distinctions" by including drugs approved and banned in both countries. However, the issue is the relative effectiveness of the two systems. If the U.S. were the first to approve a drug that was subsequently removed from the market, that is relevant (and occurred several times in the periods studied). Further, if both countries approved a drug at about the same time, it also is pertinent if the U.K. were the first to remove the product (and that occurred several times). What cannot be blurred is the fact that two significant studies examined the record over substantial periods of time, and both unequivocally concluded that the drug-approval systems in the U.K. and the U.S. have proven to be equally effective in protecting their citizens.

Dr. Wolfe also said that six additional products had been discontinued in the U.K. since the two studies were conducted. The six products will be discussed, but they represent too small a sample over too short a time to compare the U.K. and U.S. drug-approval systems. The only studies with a

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large enough data base to make a valid comparison of the two systems are the Bakke and FDA studies.

One of the six products, Zelmid, was included in the Bakke study. Another product, Osmosin, was a new sustained-release dosage form of the drug indomethacin that has been on the market in the U.S. and around the world since 1965, and is still available in this country in both regular form and in sustained-release form. Osmosin was not "banned worldwide," as Dr. Wolfe stated, but was voluntarily withdrawn when the product was said to have caused problems. The manufacturer decided not to re-introduce the product even though extensive review failed to link it to the problems, and showed that it had no more adverse effects than other anti-arthritic drugs.

Two more of the six drugs, Methrazone and Althesin, were never submitted to the FDA for approval, and thus provide no basis for comparing the relative merits of the U.K. and U.S. drug-approval systems. The other two of the six drugs, Flosint and Flenac, were submitted to, but not approved by, the FDA.

Five of the six drugs were discovered and developed by foreign-based companies in foreign countries, so removal of the U.S. export ban would not have had any impact on their development and distribution abroad. The sixth example is Osmosin, and, as has been discussed, it has been on the market in other dosage forms in the U.S. and abroad for 20 years.

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Throughout his testimony, Dr. Wolfe took the position that only the U.S. drug-approval system provides acceptable protection for its citizens. In fact, however, no system, including that of the U.S., is likely, in premarketing clinical trials, to identify adverse reactions that affect less than one patient in every 1,000 treated, and no system can possibly be careful enough to preclude all withdrawals. Along with the benefits of marketing new drugs comes the unavoidable risk of unanticipated side effects, monitored by health-care professionals, regulatory authorities, pharmaceutical manufacturers and the public. The U.S. review system addresses the risk/benefit balance differently than the U.K. system, and thus has been slower to approve new drugs. This has meant that lives may have been lost and suffering prolonged in this country because the marketing of important new drugs has been delayed. At the same time, as both the Bakke and FDA studies clearly show, the safety record of the U.S. has been no better than that of the U.K.

Following is a brief discussion of each of the 19 drugs mentioned by Dr. Wolfe in his testimony:

RECENT DRUGS

1. Zelmid: This anti-depressant, approved in the U.K. in 1982, was discovered and developed by the Swedish firm, AB Astra, in Sweden. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the drug.

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2. Osmosin: A new sustained-release dosage form of this anti-arthritic drug, approved in the U.K. in 1983, was voluntarily withdrawn from the market, but the drug (indomethacin) has been available in the U.S. and elsewhere for 20 years and remains on the market in both regular and sustained-release form.

3. Flosint: This non-steroidal anti-inflammatory drug, approved in the U.K. in 1982, was discovered and developed by the Italian firm, Pharm Italia/Carlo Erba, in Italy. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the drug.

4. Metharazone: This non-steroidal anti-inflammatory drug, which was approved in the U.K. in 1977 but was never submitted for approval to the FDA, was discovered and developed by the Italian firm, De Angeli, in Italy. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the drug.

5. Althesin: This combination anesthetic, which was approved in the U.K. in 1972 but was never submitted for approval to the FDA, was discovered and developed by the British firm, Glaxo, Inc., in Great Britain. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the drug.

6. Flenac: This non-steroidal anti-inflammatory drug, approved

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in the U. K. in 1978, was discovered and developed by the British firm, Rickitt & Coleman, in Great Britain. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the drug.

OUTDATED EXAMPLES

7. Thalidomide: This hypnotic/sedative was discovered and developed by the German company, Chemi Gruenthal, in Germany in the mid-1950s. With modern preclinical teratology testing, the likelihood of a repeat of the thalidomide tragedy is remote.

8. Isoproternol Inhalers: This substance was first marketed in the U.S. in 1948. It has been argued that a "highly concentrated" metered dosage form approved in Great Britain in the early 1960s caused deaths in asthmatic patients. The relationship between the product and increased mortality in the U.K. has been questioned in several studies (see Martindale's Extrapharmacopeia, 28th Edition, page 15, which is attached), and a comparable product with a similar amount of isoproternol base (0.112 mg vs 0.152 mg) was and is available in the U.S.

9. Aminorex: This appetite suppressant was marketed in Switzerland in the mid-1960s. The product was not approved for clinical testing in the U.K., and an IND was terminated in the U.S. in 1968.

10. Stalinon: This organic tin compound, which was used to treat

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boils, was introduced in France more than 30 years ago.

11. Chlormadinone: This oral contraceptive was approved by the FDA on April 25, 1965 and was withdrawn from the market on March 16, 1972.

12. Practolol: This cardio-selective beta blocker was introduced in the U.K. in the late 1960s, and is still available for limited use.

13. Pronethalol: This beta blocker was discovered and developed by the British firm, ICI, in the U.K. in the early 1960s. Therefore, the U.S. export ban had no bearing on the development and distribution of the drug abroad.

14. Ethynerone (MK 655): An IND was submitted to the FDA in 1963, but no record can be found that this product was ever approved for marketing or was marketed in any country.

15. Cinanserin: An IND was submitted to the FDA in 1964, but no record can be found that this product was ever approved for marketing or was marketed in any country.

16. Triflocin: An IND was submitted to the FDA in 1968, but no record can be found that this product was ever approved for marketing or was marketed in any country.

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17. Guanoxan: This anti-hypertensive, which was introduced only in Great Britain in 1964, was voluntarily removed from the market solely for business reasons.

18. Sordinol: This tranquilizer was first marketed about 25 years ago, and is still available in several European countries. According to Martindale's Extrapharmacopeia, the adverse effects and precautions for Sordinol are similar to those for chlorpromazine, which has been available in the U.S. for 31 years.

19. Hexobendine: This vasodilator was discovered and developed in 1964 by the Austrian firm, Oestereich Stickstoffwerke, in Austria. Therefore, the U.S. export ban had no bearing on the development and distribution abroad of the product.

Three of these 13 drugs (7 through 19 above) apparently were never approved for marketing or marketed in any country. Another one of the drugs was actually approved by the FDA, and a comparable product in another case also was approved by the FDA. Another drug was never approved in either the U.K. or the U.S., while still another was voluntarily removed from the market in the U.K. solely for business reasons. In all 13 cases, the drugs were approved so many years ago that the approval indicates absolutely nothing about the capabilities of the particular drug-approval authority today.

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Commentary

Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: Issues of safety

Since the modern era of drug regulation began in the early 1960s, fewer new drugs have been approved for marketing in the United States than in the United Kingdom. We examined whether information can be obtained about the relative safety of higher and lower introductory rate policies by comparing each country's record of drugs that have been discontinued (removed from the market, withdrawn, or whose licenses were allowed to lapse) while a question of safety existed. We have compiled a list of both older (approved before 1964) and newer (approved in 1964 or later) chemical entities discontinued in the last two decades. With the aforementioned broad criteria to define "discontinuation," and to assess whether a question of safety was involved, our study showed that a total of 24 chemical entities have been discontinued in the United States or the United Kingdom. Nearly half (10 drugs) were products that had been approved in both countries, while the remainder (drugs that had been exclusively available in one country or the other) consisted of four drugs in the United States and 10 in the United Kingdom. Among the drugs introduced during the last two decades, five have been discontinued in the United States and eight in the United Kingdom. Each country's record of discontinuations has been remarkably similar for drugs introduced after 1974: Four have been discontinued in the United States and three in the United Kingdom. Since drugs discontinued while a safety question existed represent only 2% of the new chemical entities introduced, it appears that drugs that reach the market under the prevailing regulatory systems are seldom associated with unacceptable toxicity.

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A preliminary report of these results was presented at the Nineteenth Annual Meeting of the Drug Information Association, Washington, D.C., July 30, 1983.

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The drug approval process differs in the United Kingdom and the United States, with the U.S. system characterized as more demanding and time consuming. Over the past two decades, fewer new drugs have been approved in the United States, usually with a delay in those that are approved.[3, 4, 9, 13] On the one hand, the more lengthy and complex approval process in the United States and the ensuing drug lag have deprived patients in the United States of a number of useful and even life-saving medicines. On the other hand, it can be argued that the more restrictive U.S. policy has resulted in more protection from drug-related toxicity, although this benefit has so far not seemed to outweigh the costs.[13]

One can obtain some indications about the relative safety of a policy of early and higher introduction rate by examining each country's record of drugs that, for some safety reason, have been discontinued or removed or withdrawn from the market. The current policies of drug review date from revisions in the early 1960s in the aftermath of the thalidomide tragedy. We chose January 1, 1964, as the starting date for our observations for the following reasons. Whereas preregistration review of toxicity and safety data had been practiced for many years in the United States, it was not until the 1962 Drug Amendments that efficacy requirements were introduced along with obligation on the part of the manufacturers to report information on adverse reactions to the Food and Drug Administration (FDA). In the United Kingdom, voluntary prereview came into effect with the establishment of the Committee on Safety of Drugs in 1963 and its registry of adverse reactions, which started early in 1964.[14]

We are primarily interested in the comparison of drug introductions and discontinuations during the period when both countries had implemented modern drug regulations—hence the date January 1, 1964. Since regulatory policies also differed earlier, we have included in our study both older (introduced before 1964) and newer (introduced in 1964 or later) drugs.

Methods

Sources of information. Since there are no published lists of drug discontinuations for safety reasons either in the United Kingdom or the United States, we started by screening successive editions of standard textbooks of pharmacology (1955 to 1982), review articles, and textbooks that covered adverse drug reactions reported between 1960 and 1983.[1, 2, 5, 7, 10, 13, 14] A computer search was performed on the literature base of the Center for the Study of Drug Development, through the library of Excerpta Medica, and through the Pharmaceutical News Index, of which the main sources are SCRIP (United Kingdom) and the FDC Reports ("The Pink Sheet," United States). Data on drug introductions in the United States were obtained from the *Physicians' Desk Reference*, 1954 to 1983, name and product surveys,[3, 9] and from a published summary of the Kennedy hearings.[12] Important sources of information with regard to the British market were successive editions (1955 to 1982) of *Martindale, The Extra Pharmacopoeia*,[11] the Data Sheet Compendium of the Association of the British Pharmaceutical Industry, and a complete collection of *The Pharmaceutical Journal* from the period studied that contained data on drug introductions and discontinuations and published statements of the Committee on Safety of Drugs. Wherever there was doubt about whether or not adverse effects were associated with the discontinuation, we asked other sources, including the sponsoring companies, for information.

Scope and definitions. While it is simple to state the question in which we were originally interested (i.e., What drugs have been withdrawn for safety reasons in each country?), defining the particulars in a manner suitable for use in a comparative analysis proved to be more difficult because of the scope and meaning of the terms "withdrawal," "drug," and "safety reasons."

When a drug ceases to be marketed, it is often difficult to determine whether it has been "withdrawn" (ie, the license simply allowed to lapse) by the manufacturer or "removed" by the regulatory agency. Such an action is usually a combination of both, and infinite gradations and combinations are possible. In addition, there are "recalls," usually caused by technical problems with a particular batch, but inherent problems with the method of manufacture may

occasionally result in permanent withdrawal of a product (e.g., polidexide). Furthermore, in the United States a drug may be withdrawn from the market without having its new drug application (NDA) withdrawn, so that the official list of NDA withdrawals does not exactly suit our interests. For these reasons, we chose to make our criterion the discontinuation of a drug's marketing, regardless of whether this discontinuation was initiated by the drug's sponsor or by the regulatory agency and regardless of whether the discontinuation was voluntary or involuntary on the part of the sponsor. Temporary withdrawals with later reintroductions (e.g., tranylcypromine and alphaprodine) were not regarded as discontinuations under our criterion. Drugs were included in the list (Table I) if withdrawn and subsequently reintroduced only for a new and more serious indication for which some toxic reactions may represent an acceptable risk (e.g., aminoglutethimide and megestrol reintroduced for the treatment of hormone-dependent neoplasms).

The nature of the restrictive action is also important. Initially, our study was primarily focused on the total discontinuation of a drug as a separate chemical entity. Cases exist, however, of drugs that have been discontinued in one dose formulation but not another (e.g., oral practolol and enteric-coated potassium chloride preparations); for one indication but not another; or in one combination but not another. We therefore chose not to regard combination formulations as separate drug entities in our study. For example, the recently withdrawn antiemetic preparation Bendectin/Debendox (Merrell Dow), which contained doxylamine and pyridoxine, as well as dicyclomine in the United Kingdom, is not included in the present list of discontinued drugs because the active principles are still on the market alone or in other combinations. Discontinuations of particular dosage forms are only included in the list if they represent the major use of the drug (e.g., oral practolol; the parenteral form is still available) or widespread application of a therapeutic principle (e.g., oral clioquinol for diarrhea; the topical form is still available). We have not included the sweetener cyclamate, since its widespread use as a food additive for the general population, not its use as a "drug" for diabetes, was the major concern leading to its withdrawal.

It was often particularly difficult to determine whether a drug was "discontinued for a safety reason." The question of safety was usually inseparable from that of the drug's efficacy for its intended use, and often the question of commercial viability was involved as well. Furthermore, the question of proof of causation is extremely difficult, particularly because once a drug has been withdrawn from the market—even as a precautionary measure—final proof or disproof of the drug's causal association with the suspected toxic effect may be precluded. We did not attempt to evaluate whether or not the discontinuations were justified on safety grounds.

Although safety is the issue of interest, it is often inseparable from the question of efficacy. In the case of the arrival of a new, safer, more effective and therefore better-selling drug on the market, we did not conclude that discontinuation of the older equivalent with more pronounced side effects occurred for safety reasons. For example, the discontinuation of nalorphine after the introduction of naloxone was not considered to be for safety reasons. Therefore, we chose to use a broad criterion in the evaluation of drug discontinuations for inclusion in this study, namely drugs in whose discontinuation "a question of safety was involved," regardless of whether this was the sole or major reason for discontinuation and regardless of whether the causal association was believed to have been finally proved.

Even with this broad definition, considerable latitude exists and judgment is required, as in the following examples: The monoamine oxidase (MAO) inhibitors are associated with not inconsiderable incidence of liver damage and adverse interactions with other drugs and food constituents. A warning was issued by the Committee on Safety of Drugs about the side effects associated with all of the MAO inhibitors on the U.K. market in 1964.[14] We therefore considered a safety question to be a significant factor in the subsequent discontinuation of any such drugs, even though it was not explicitly stated in all cases.

Estrogens and progestogens used as sequen-

Table 1. *Drug discontinuations in which a question of safety was involved, 1964 to 1983*

Drug	Trade names*	U.K.		U.S.	
		Introduction	Discontinuation	Introduction	Discontinuation
Alclofenac	Prinalgin	1972	1979	NM	—
Aminoglutethimide†	Elipten	NM	—	1960	1966
Aminopyrine	(numerous)	c. 1900	c. 1975	c. 1900	c. 1970
Azaribine†	Triazure	NM	—	1975	1976
Benoxaprofen	Opren, Oraflex	1980	1982	1982	1982
Benziodarone	Amplivix, Cardivix	1962	1964	NM	—
Chlormadinone†	Normenon, Verton C-Quens, Sequence	1966	1970	1965	1970
Clioquinol (oral)	Entero-Vioform	c. 1930	1981	c. 1930	c. 1973
Dipyrone	(numerous)	c. 1930	c. 1975	c. 1930	1977
Ibufenac	Dytransin	1966	1968	NM	—
Mebanazine	Actomol	1963	1975	NM	—
Megestrol†	Volidan 21, Serial 28	1963	1970	NM	—
Methapyrilene	(numerous)	c. 1950	1979	1947	1979
Nialamide	Niamid	1959	1978	1959	1974
Oxyphenisatin	(numerous)	c. 1955	1978	1957	1972
Phenacetin	(numerous)	c. 1900	1980	c. 1900	1983
Phenformin	Dibotin	1959	ND	1959	1977
Phenoxypropazine	Drazine	1961	1966	NM	—
Polidexide	Secholex	1974	1975	NM	—
Practolol (oral)	Eraldin	1970	1976	NM	—
Pronethalol	Alderlin, Nethalide	1963	1965	NM	—
Ticrynafen	Selacryn	NM	—	1979	1980
Zimelidine	Zelmid	1982	1983	NM	—
Zomepirac	Zomax	1981	1983	1980	1983

NM = not marketed; ND = not discontinued.

The inclusion of a drug in this table does not necessarily indicate a proved causal relationship to the toxic effects cited (see text). For some older drugs only the approximate time of introduction is available; several such drugs were gradually phased out around the year indicated.

*Only most commonly prescribed trade names used.

†Reintroduced for treatment of hormone-dependent malignant tumors (see text).

tial oral contraceptives, combination pills, or as hormonal pregnancy tests represent a particularly complex area in which a number of drugs have been withdrawn or reformulated.[5] Numerous combinations have been marketed and some preparations have also been used for other indications, e.g., menstrual disorders and hormone-dependent malignant diseases. Since we were mainly interested in separate chemical entities, only two substances (chlormadinone and megestrol) are included in our list. Both of these compounds produced breast tumors in beagle dogs when given in high doses in chronic toxicity tests.

Therapeutic class	*Alleged safety question*
Anti-inflammatory	Skin rash, systemic vasculitis
Anticonvulsant	Endocrine disorders
Analgesic, antipyretic	Bone marrow suppression
Antipsoriatic	Thromboembolism
Anti-inflammatory	Liver damage, skin rash, photosensitivity
Coronary vasodilator	Jaundice
Progestogen, oral contraceptive	Tumors in beagle dogs
Antidiarrheal, antiamoebic	Neurotoxicity
Analgesic, antipyretic	Bone marrow suppression
Anti-inflammatory	Jaundice, liver damage
Antidepressant, MAO inhibitor	Liver damage, interactions
Progestogen, oral contraceptive	Thrombosis in beagle dogs
Hypnotic, antihistaminic	Cancer in rats
Antidepressant, MAO inhibitor	Liver damage, interactions
Laxative	Liver damage
Analgesic, antipyretic	Nephropathy
Antidiabetic	Lactic acidosis
Antidepressant, MAO inhibitor	Liver damage, interactions
Hypolipidemic	Toxic impurities
β-Blocker	Oculomucocutaneous syndrome
β-Blocker	Thymic tumors in mice
Diuretic	Liver damage
Antidepressant	Neuropathies, convulsions, liver damage
Analgesic, antipyretic	Anaphylactic shock, renal failure

Thus, although our original question was simple, in practice the criteria cannot be simply applied given the present state of knowledge, and interpretation is often needed as to whether or not a drug should be included in this list. This difficulty reflects the complex issues involved in the discontinuation of drugs.

Results

Drugs discontinued in light of a safety question (see Methods) either in the United Kingdom, the United States, or both markets are listed in Table I. The main safety questions are also listed, although, as described above, the decision to discontinue the products was often the result of complex features including several different problems. The dates of introduction to the market and of discontinuation are also given. Some substances (e.g., phenacetin and the aminopyrine-type analgesics) were introduced so long ago that the exact year of introduction cannot be ascertained, and they were gradually phased out over a number of years.

Since requirements for marketing approval increased substantially in the early 1960s with the introduction of new regulations, we have classified the drugs by year of introduction (Table II). Seven of the older drugs introduced before 1964 were discontinued in both the United Kingdom and the United States during the following two decades, whereas those withdrawn only in the United Kingdom or in the United States numbered five and two. Among the drugs introduced in 1964 and after, three were approved and subsequently discontinued on both markets, while an additional five drugs were approved and withdrawn in the United Kingdom compared to two exclusively approved and withdrawn in the United States. A pooling of data from drugs introduced before 1964 and 1964 and after reveals that the total number of older and newer drugs discontinued in both countries is 10, plus an additional 10 drugs introduced and withdrawn exclusively in the United Kingdom and four such drugs in the United States, which makes the respective totals 20 and 14.

Oral contraceptives and related drugs proved particularly difficult for us to classify in this paper because they are usually given in combination and usually used for other indications as well. Whereas only two progestogens (chlormadinone and megestrol) are listed in Table I, it should be noted that there were other major safety issues in the hormonal area, related not so much to the molecules themselves as to dose (estrogen content of oral contraceptives), mode of use (sequential vs combination pills), and indications (e.g., hormonal pregnancy tests). Some sequential oral contraceptives that caused tumors in beagle dogs (medroxyprogesterone/

Table II. *Drug discontinuations by times of introduction*

Before 1964			*1964 and later*		
Both U.S. and U.K. (n = 7)	*U.K. only (n = 5)*	*U.S. only (n = 2)*	*Both U.S. and U.K. (n = 3)*	*U.K. only (n = 5)*	*U.S. only (n = 2)*
Aminopyrine	Benziodarone	Aminoglutethimide	Benoxaprofen	Alclofenac	Azaribine
Clioquinol	Mebanazine	Phenformin	Chlormadinone	Ibufenac	Ticrynafen
Dipyrone	Megestrol		Zomepirac	Polidexide	
Methapyrilene	Phenoxypropazine			Practolol (oral)	
Nialamide	Pronethalol			Zimelidine	
Oxyphenisatin					
Phenacetin					

ethinyl estradiol) or were suspected of being associated with increased incidence of endometrial tumors (dimethisterone/ethinyl estradiol) were discontinued. We considered these cases, along with the diagnostics next described, to be examples of hazards in dose presentation form or usage rather than as intrinsic hazards in the chemical entities themselves. Clearly, however, this is an area where there is room for judgement. Combinations of high doses of norethisterone or ethisterone with ethinyl estradiol were promoted as a test for pregnancy and later discontinued both in the United States and the United Kingdom because of evidence suggesting that this use was associated with birth defects. Apart from the withdrawal resulting from questions about both safety and efficacy of all sequential oral contraceptives in the United States at the request of the FDA and the introduction and subsequent discontinuation of megestrol in the United Kingdom, it appears that there have been no major differences between the policies of the United Kingdom and the United States with regard to oral contraceptives and hormonal pregnancy tests.

It should be noted that some well-known examples of drug toxicity occurred just before the advent of the new regulations (and indeed prompted the changes in regulations in some cases) or in the transitional period. These drugs, which are not shown in the tables, include thalidomide, amphenidone, thenalidine, furaltadone, zoxazolamine, triparanol, etryptamine, iproniazid, pheniprazine, and pivhydrazine.

Discussion

The main conclusion to be drawn from our survey is that drugs that reach the market under the prevailing regulatory systems in the United States and the United Kingdom are seldom judged to be unsafe by the criteria we have used in this study. Published data on the introduction of new chemical entities[3, 9] indicate that the mean number of new drugs marketed per year in the 1970s was approximately 16 in the United States and 21 in the United Kingdom. Overall, the drugs that were subsequently discontinued in light of safety questions represent only 2% of the drugs introduced on the market.

Although the number of drug discontinuations is slightly higher in the United Kingdom than in the United States (totals 20 and 14; eight and five in 1964 or later), the number of drugs approved in the United Kingdom is also higher, and the present survey has not revealed large differences between the two countries. It is noteworthy that the differences that do exist stem from the early years of the period surveyed; most of the new chemical entities withdrawn exclusively from the United Kingdom were introduced there between 1962 and 1974 (benziodarone, megestrol, pronethalol, ibufenac, alclofenac, and polidexide). Among the drugs introduced after 1974, two (zomepirac and benoxaprofen) were marketed and subsequently discontinued in both countries, whereas only one exclusively available chemical entity has been withdrawn in the United Kingdom (zimelidine) and there were two such withdrawals in the United States (azaribine and ticrynafen). Therefore, while a number of subsequently discontinued drugs were marketed exclusively in the United Kingdom in the 1960s and early 1970s, the number of withdrawals for reasons of safety during the most recent decade has been low and remarkably similar to that in the United

States, despite the larger number of drugs approved in the United Kingdom.

The reasons for removal or withdrawal of drugs are seldom scientifically indisputable, and there is no guarantee that the "toxic threshold" of the regulatory agencies, the firms, the medical community, or even the general public is the same in each country. However, because of the substantial publicity given to drug toxicity problems and the resultant public pressure on drug firms and regulatory agencies alike, and also the international communication between the medical communities and the drug regulatory agencies, it is likely that the thresholds for removing a drug from the market in the United Kingdom and the United States may now be more similar than are the criteria for introducing drugs to the market. This notion is supported by the finding that among the drugs introduced in both countries, the only difference in removals during the last two decades is phenformin, which is still available in the United Kingdom while discontinued in the United States.

Discontinuation in marketing a drug is not the only restrictive action that can be taken against a drug, as already discussed. Other restrictive actions that regulatory agencies take in response to questions about drug safety include warnings of adverse effects, restrictions on dose, dosage forms, indications, and prescription, and restrictions on the use of "inactive" drug constituents (Table III). Obviously, therefore, our comparison of drug discontinuations illustrates only one aspect of drug surveillance and regulation. Since we could not obtain complete data on the incidence of these less drastic restrictive measures, we cannot determine whether the two countries are similar in this respect.

The role of safety in an individual drug withdrawal is often hard to specify. Unlike the clear-cut situation in which a large number of major congenital defects were discovered after maternal use of thalidomide in 1959 and 1960, the circumstances that led to the discontinuation of marketing were complex and arguable for most of the entities included in the present study.

The impact of drug toxicity and the measures taken to combat it depend on the severity of the side effects, the period of time a potentially unsafe drug is on the market before withdrawal,

Table III. *Examples of other regulatory measures involving safety considerations*

Warnings of adverse effects
Barbiturates, propoxyphene, and clofibrate
Restrictions on dose and dosage forms
Decreased strength of β_2-adrenergic sprays, lowering of estrogen content of oral contraceptives, and practolol only for parenteral use
Restrictions on indications
Amphetamine, not to be used for obesity, diethylstilbestrol not to be used for threatened abortion, chloramphenicol not to be used for common and recurrent infections
Restrictions on prescription
Over the counter vs prescription only, general release vs hospital use only, and controlled substances
Restrictions on use of "inactive" drug constituents
Ban of urethane and chloroform in parenteral preparations and of certain dyes in tablets and capsules

and the number of patients treated in a manner that yields toxic effects. Other factors that must be taken into account include the beneficial therapeutic effect of the drug involved and whether or not alternative, safer drugs are available.

On the whole there is no single, fully accepted cause for discontinuation of most of the drugs in Table I. Even for practolol, the drug with perhaps the clearest evidence of serious side effects related to use at recommended doses, the beneficial effects under conditions of use that could be defined today (for example, in prevention of death after myocardial infarction) would outweigh the adverse reactions if alternative and safer β-blockers had not become available. The results of a recent survey in which 20 leading British physicians and high-ranking regulatory agency personnel in various countries were each asked to list the 10 most important adverse drug reactions since thalidomide illustrate the complexity of the issue.[13] Out of the 24 drugs in Table I, only practolol, phenformin, and MAO inhibitors appeared among the top 31 on the lists of drugs most frequently mentioned as causing important adverse effects.

Although ideally one might wish that drug withdrawals should never be necessary, in practice some will always be needed, if only because the full facts about a drug's effects—beneficial as well as harmful—can never be

known at the time of marketing. There is no simple answer to the question of what is an acceptable rate of drug discontinuation for safety reasons. One should expect a certain percentage of approved drugs to require removal for safety reasons as the price to pay for policies that are not excessively restrictive and do not deprive patients of important therapeutic benefits by delaying indefinitely the introduction of new medicines.

The data we obtained can also be used to examine the reasons for withdrawal, and to determine whether, for example, there has been any change over time in the type of toxicity that gives rise to safety questions. The role of animal toxicity data as compared to human side effects seems to have shifted during the period covered by the present study. Most of the early withdrawals, i.e., before 1970, were related to reports of side effects in patients. Since 1970, however, a number of drugs have been discontinued in light of benign or malignant tumors that appear after chronic exposure in animals. After 1980 all drug discontinuations have been in association with data from clinical use.

It is striking that three of the products most recently discontinued were drugs with high sales volumes. Benoxaprofen, ticrynafen, and zomepirac were heavily promoted and very rapidly accepted by physicians after introduction. It is possible that the present drug surveillance schemes and follow-up of reported side effects are biased to raise alarms for medicines that are often prescribed, and that they are less likely to question the safety of less successful products.

It might be possible to extend the approach adopted in this article to make a more comprehensive comparison of the safety performance of the two regulatory systems. That would require an exhaustive quantitative assessment, including a detailed risk/benefit analysis that involved consideration of such facts as how long the discontinued drugs were available on each market and the number of patients treated both appropriately and inappropriately. It is unlikely that the necessary details will be readily obtainable. To the extent that the data currently available can be used to answer the question, however, it appears that drugs approved under modern regulations are seldom associated with unacceptable toxicity, and that the U.S. system of approval, in spite of its greater restrictiveness and insistence on detail, has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions.

Authors' note added in proof

After the acceptance of this article, another anti-inflammatory drug, indoprofen, was withdrawn in the United Kingdom because of side effects (Lancet, Dec. 17, 1983, p 1436).

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OPE STUDY 68

NEW DRUG INTRODUCTIONS, DISCONTINUATIONS, AND SAFETY ISSUES IN THE UNITED STATES AND THE UNITED KINGDOM 1960-1982

January 1984

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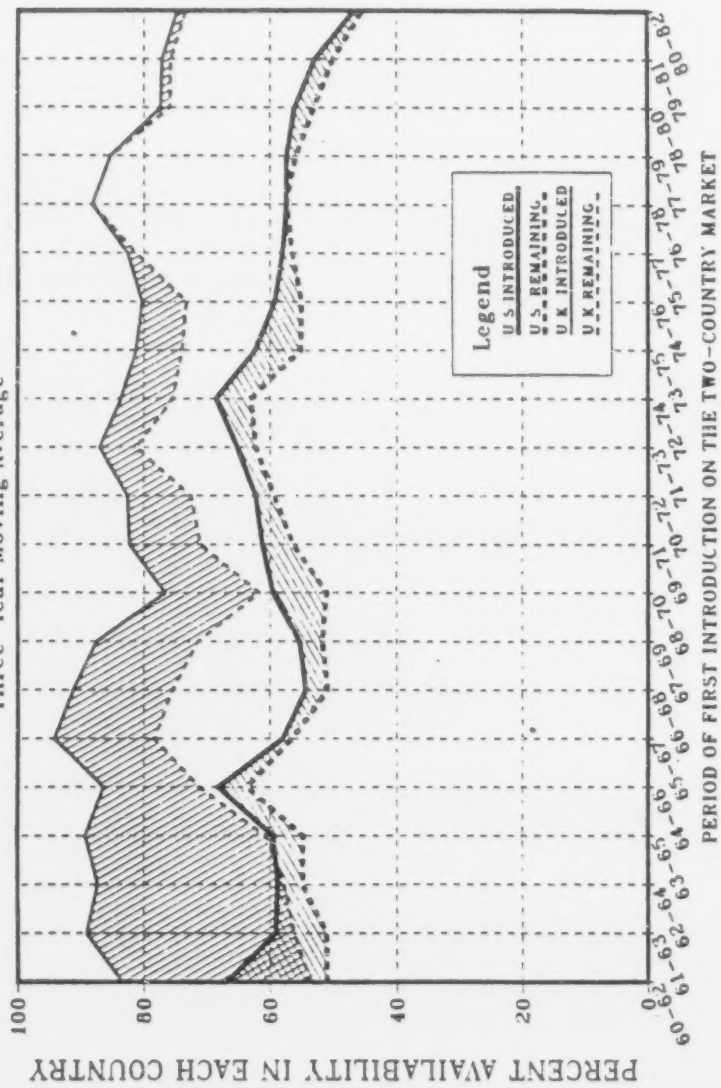
JANUARY 1984 FDA STUDY

FIGURE 2

PERCENT OF NCE'S FIRST INTRODUCED ON TWO-COUNTRY MARKET IN SPECIFIED PERIOD AND REMAINING ON MARKET AS OF 12-31-82

Three-Year Moving Average



JANUARY 1984 FDA STUDY

5

SUMMARY OF FINDINGS

A detailed analysis of the introduction and discontinuation dates for new chemical entities on the U.S./U.K. two-country market from 1960 through 1982 shows the following.

- More NCEs are introduced on the U.K. market than the U.S. market. However, a higher proportion of the NCEs marketed in the U.K. are discontinued compared to the U.S. market. For every consecutive three-year period between 1960 and 1977, the number and percentage of discontinued NCEs is higher for the U.K.

- Discontinued NCEs show a strong relationship with the passage of calendar time in the U.K. In the U.K. 33.3 percent of the NCEs from the period 1961 through 1965 had been discontinued by the end of 1982. For NCEs first marketed after 1974, only 1.3 percent had been discontinued. This pattern is not nearly as apparent for NCEs marketed in the U.S. Comparable statistics for the U.S. are 11.6 percent and 3.1 percent. In fact, the percentage of NCEs first marketed between 1962 and 1976 and subsequently discontinued remains remarkably constant at about 6.5 percent for the U.S.

- The net result of the total number of introduced and discontinued NCEs (those remaining on the market at the end of 1982), tends to converge for the two countries as calendar time progresses. This equality of total numbers doesn't imply that the two sets of NCEs are identical. However, there is some tendency toward increased similarity.

- Only 14 of the 614 NCEs introduced since 1960 were the subject of documented safety discontinuations on the U.S./U.K. two-country market. These 14 NCEs accounted for eight safety discontinuations in the U.S. and 10 safety discontinuations in the U.K.

- Most documented safety discontinuations occurred within two years of introduction. In contrast, the mean market life for discontinuations not associated with safety was about 11 years.

- Discontinuations, both total and documented safety are more heavily concentrated among NCEs first marketed in the early 1960's than those first marketed after 1963.

JANUARY 1984 FDA STUDY

These findings demonstrate that analyses of drug discontinuations as well as introductions are important elements in the study of new drugs. The culmination of drug development, drug regulation, drug marketing and prescribing in the U.K. allows more NCEs on the market quicker, but results in significantly more discontinued NCEs within a fixed time period. The process in the U.S. accounts for relatively fewer NCEs on the market somewhat later, but the NCEs have a lower probability of discontinuation resulting in longer product lives.

The conclusion that documented major safety issues are not the primary reason for large differences in discontinuation rates demonstrates the need to closely examine other factors that may be accounting for the differences.

(Hydrochloride)

An almost white very hygroscopic crystalline powder. M.p. about 68°. **Soluble** in water and alcohol. **Store** in airtight containers.

2073-n

Isometheptene Mucate. Isometheptene galactarate.

$(C_9H_{19}N)_2.C_6H_{10}O_8 = 492.7$

CAS — 7492-31-1

A white crystalline powder with a bitter taste. Freely **soluble** in water, soluble in alcohol; practically insoluble in chloroform and ether. A 4.95% solution in water is iso-osmotic with serum.

Adverse Effects, Treatment, and Precautions. As for Adrenaline, pp 2-3.

Uses. Isometheptene is a sympathomimetic agent which has been advocated for the relaxation of spasms. It has been given as the hydrochloride and as the mucate. It is given for a vasoconstrictor effect in migraine.

Migraine. Comment on the value of a preparation containing isometheptene mucate in the management of migraine — *Drug & Ther. Bull.*, 1972, *10*, 64. Further references — P. O. Behan, *Practitioner*, 1978, *221*, 937.

Proprietary Preparations

Midrid Capsules *(Carnrick, UK)*. Each contains isometheptene mucate 65 mg, dichloralphenazone 100 mg, and paracetamol 325 mg. *Dixie.* For migraine headaches, 2 capsules initially, followed by 1 capsule every hour up to a maximum of 5 capsules in 12 hours; for tension headaches, 2 capsules initially, followed by 1 or 2 capsules every 4 hours up to a maximum of 8 capsules per day.

Other Proprietary Names

Octinum (hydrochloride and mucate) *(Ital., Switz.)*.

2074-h

Isoprenaline Hydrochloride *(B.P.)*. Isoprenalini Hydrochloridum; Isoproterenol Hydrochloride *(U.S.P.)*; Isopropylarterenol Hydrochloride; Isopropylnoradrenaline Hydrochloride. 1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride.

$C_{11}H_{17}NO_3.HCl = 247.7$.

CAS — 7683-59-2 (isoprenaline); 51-30-9 (hydrochloride).

Pharmacopoeias. In *Arg., Br., Braz., Chin., Hung., Int., Roum., Turk.*, and *U.S.*

A white or almost white, odourless or almost odourless, crystalline powder with a slightly bitter taste. It gradually darkens on exposure to air and light. M.p. 165° to 170° with decomposition. **Soluble** 1 in less than 1 of water and 1 in 50 to 55 of alcohol; less soluble in dehydrated alcohol; practically insoluble in chloroform and ether. A 1% solution in water has a pH of about 5. Solutions are **sterilised** by filtration and stored in ampoules, the air in which is replaced by nitrogen or other suitable gas. Solutions become pink to brownish-pink on standing exposed to air and almost immediately so when made alkaline. **Store** in airtight containers. Protect from light.

2075-m

Isoprenaline Sulphate *(B.P.)*. Isoprenalini Sulfas; Isopropylarterenol Sulphate; Isopropylnoradrenaline Sulphate; Isoproterenol Sulfate *(U.S.P.)*.

$(C_{11}H_{17}NO_3)_2.H_2SO_4.2H_2O = 556.6$.

CAS — 299-95-6 (anhydrous); 6700-39-6 (dihydrate)

Pharmacopoeias. In *Br., Cz., Fr., Ger., ind., Int., It., Neth., Nord., Pol., Swiss, Turk.*, and *U.S.*

A white or almost white, odourless or almost odourless, crystalline powder with an astringent and somewhat bitter taste. It gradually darkens on exposure to light and air. M.p. about 128° with decomposition. **Soluble** 1 in 4 of water, slightly soluble in alcohol; practically insoluble in chloroform and ether. A 1% solution in water has a pH of 4 to 5.5. A 0.65% solution in water is iso-osmotic with serum.

Solutions are **sterilised** by autoclaving or by filtration. Solutions become pink to brownish-pink on standing exposed to air, and almost immediately so when made alkaline. Solutions should contain sodium metabisulphite as an antioxidant and should not be allowed to come into contact with metal, which causes discoloration and loss of activity; solutions for inhalation should be used in all-glass atomisers. **Store** in airtight containers. Protect from light.

Stability. The addition of sodium metabisulphite 0.1% reduced the discoloration and deposition of particles in an injection containing isoprenaline sulphate 0.03% in water, water adjusted to pH 3 with hydrochloric acid, or in McIlvaine's citrate-phosphate buffer solution, pH 3. Solutions made using the buffer were more stable than those adjusted with acid. Autoclaving a solution adjusted with hydrochloric acid to pH 3 led to a 30% loss of potency. If sodium metabisulphite or McIlvaine's buffer solution was used the loss was about 3%. During storage, solutions sterilised by filtration lost no potency at 0° to 4°, about 2 to 10% at 25° over 24 weeks, and 5 to 23% at 37° over 8 weeks. A 0.02% injection of isoprenaline sulphate containing sodium metabisulphite 0.1%, buffered to pH 3 and sterilised by filtration, could be expected to maintain its appearance and potency for up to 6 months when stored in a refrigerator. — Pharm. Soc. Lab. Rep. P/77/2, 1977.

Adverse Effects. Side-effects associated with isoprenaline include nervousness, tachycardia, palpitations, and precordial pain. Other side-effects are hypotension with dizziness and fainting, headache, flushing of the skin, cardiac arrhythmias, tremor, weakness, and nausea and vomiting. Sweating may occasionally occur.

In the late 1960s, reports from many parts of the world indicated that the mortality-rate in patients suffering from asthma was increasing, particularly in asthmatics below 20 years of age. Sudden and unexpected death in asthmatics was also becoming more frequent and in many cases had followed excessive use of aerosols of bronchodilator drugs. Following warnings, use of the aerosols and deaths from asthma declined again. Because of the risk of tolerance and severe bronchoconstriction and the possibility of sudden death following the excessive use of sympathomimetic agents in aerosol form, the instructions for dosage should be followed carefully (see Uses, p 16).

Prolonged use of isoprenaline may lead to resistance, and eventual deterioration, with hypoxia in asthmatic patients.

Prolonged use of isoprenaline tablets sublingually has been reported to cause severe damage to the teeth.

Bronchospasm. Twelve of 41 patients with intractable asthma who were known not to be isoprenaline abusers developed paradoxical bronchospasm after inhalation of isoprenaline. They had not used isoprenaline aerosol for a year prior to evaluation. Furthermore, they consistently showed the expected bronchodilatory response when repeatedly challenged with terbutaline aerosol. — J. Tranter *et al.*, *Chest*, 1976, *70*, 711. Discussion on the possible reason for such a paradoxical response (including a possible reaction to the aerosol propellent), and comments on the need for further information. — J. W. Jenne and T. W. Chick, *ibid.*, 691.

Effects on the heart. Investigations in 10 healthy subjects indicated that induced respiratory acidosis could alter the usual cardiovascular effects of isoprenaline given intravenously. — C. Xanalatos *et al.*, *Clin. Pharmac. Ther.*, 1973, *14*, 21.

The cardiac effect of repeated inhaled doses of isoprenaline was studied in 18 patients with moderate to severe asthma. Only 1 patient experienced a significant increase in heart-rate immediately after a therapeutic dose of isoprenaline. Arrhythmias did not develop even after repeated inhalations every 5 minutes. — S. Shim and M. H. Williams, *Ann. intern. Med.*, 1975, *82*, 208. See also J. W. Patterson *et al.*, *Lancet*, 1968, *2*, 426.

A review of patient records revealed 8 cases of documented isoprenaline cardiotoxicity at therapeutic dosages. Two patients developed acute myocardial infarction, a 15-year-old child developed reversible subendocardial ischaemia on receiving an isoprenaline infusion following cardiac surgery, and 5 patients with bronchial asthma demonstrated periods of transient myocardial ischaemia. — T. Winnie *et al.*, *Am. Heart J.*, 1975, *89*, 814.

Individual reports of adverse effects of isoprenaline on the heart: J. R. Matson *et al.*, *J. Pediat.*, 1978, *92*, 776 (myocardial ischaemia in a child); G. Barland *et al.*, *J. Allergy & clin. Immunol.*, 1979, *63*, 407 (myocardial necrosis).

Animal studies on the adverse effects of isoprenaline on the heart, including induction of cardiac necrosis: M. F. Lucken, *Lancet*, 1965, *2*, 104; G. P. Lesykowsky and G. Gál, *J. Pharm. Pharmac.*, 1967, *19*, 276; T. Bálazs *et al.*, *Toxic. appl. Pharmac.*, 1971, *20*, 402; D. G. McDevitt *et al.*, *Br. J. Pharmac.*, 1974, *50*, 335.

Effects on the teeth. A 12-year-old girl, who had been taking isoprenaline sulphate tablets sublingually for 6 years, developed discoloration and destruction of her permanent incisor and canine teeth. They were discoloured a chalky-white with a loss of the natural enamel translucency. Similar results were obtained with experimental teeth when they were immersed for 2 weeks in a solution of isoprenaline sulphate. — J. S. Ball (letter), *Br. med. J.*, 1965, *1*, 1189.

Overdosage. A 66-year-old patient who had been taking up to 260 mg of isoprenaline daily as sublingual tablets for bronchitis developed tremors, incoordination, a disturbing sleep pattern, and deep ulceration of the tongue. When isoprenaline was withdrawn the patient improved and after 4 weeks the ulcer had healed. — R. D. Brown and G. Bolas, *Br. dent. J.*, 1973, *134*, 336.

For controversy surrounding the role of overuse of isoprenaline aerosols and sudden death in asthmatics, see under Sudden Death (below).

Pulmonary oedema. For reference to pulmonary oedema associated with regimens incorporating beta sympathomimetic drugs for the prevention of premature labour, see Ritodrine Hydrochloride, p 28, and Terbutaline Sulphate, p 32.

Sudden death. Between 1961 and 1966, rapid growth in the sales of pressurised aerosols of sympathomimetics in England and Wales corresponded with an increase in mortality due to asthma. The increase was greatest in children aged 10 to 14 years. Since March 1967, there had been a sharp fall in deaths due to asthma, together with a reduction in the use of pressurised aerosols. — W. H. W. Inman and A. M. Adelstein, *Lancet*, 1969, *2*, 279. See also H. E. Lewis, *Riker* (letter), *ibid.*, 799; *ibid.*, 800. For a similar report for Eire, see W. D. Linehan (letter), *Br. med. J.*, 1969, *4*, 172.

Comment on the surge in asthma fatalities that occurred in the 1960s and the growing realisation that pressurised aerosols were probably not the main culprit. — *Lancet*, 1979, *2*, 337. Strong disagreement with the view that the evidence is declining that pressurised aerosols were reponsible for the epidemic of asthma deaths in the 1960s. — P. D. Stolley and R. Schonnar (letter), *ibid.*, 897. Overuse of isoprenaline aerosols results in tolerance, not toxicity and the conclusion from this and other data can only be that the rise and fall of asthma mortality has a multifactorial aetiology which is only partly known. — H. Herxheimer (letter), *ibid.*, 1084. Following a general alert and warning on aerosol canisters, asthma mortality quickly declined to its former level. — A. M. Adelstein (letter), *Lancet*, 1979, *2*, 1247.

Early information from the British Thoracic Association's confidential enquiry into asthma deaths has indicated that, in general, patients die from asthma rather than from its treatment. When excessive use of bronchodilators does occasionally coincide with asthma death, it is likely that this indicates the need for further treatment by other drugs such as corticosteroids and is not itself the cause of death. — C. J. Stewart *et al.* (letter), *Lancet*, 1981, *2*, 747.

For earlier references to asthma fatalities in patients using isoprenaline aerosols, see Martindale 27th Edn, p 16.

For a discussion on the avoidance of asthma fatalities with emphasis on the importance of the prompt treatment of severe acute asthma, see Corticosteroids, p 453.

Treatment of Adverse Effects. Most toxic effects of isoprenaline subside rapidly when treatment is stopped. Tachycardia and cardiac arrhythmias induced by isoprenaline may be diminished by

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